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## GEOGRAPHIC PATTERNS OF CANCER MORTALITY IN THE UNITED STATES

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### INTRODUCTION

The geographic variation in cancer mortality in the United States usually has been evaluated on a state-by-state basis. The paucity of clues arising from such surveys can be traced to the heterogeneity of statewide populations. Recently, we acquired 20 years of cancer mortality data (1950-1969) for the 3,056 individual counties of the contiguous United States [1]. Counties may represent an ideal compromise between the need for units small enough to be homogeneous for demographic and environmental characteristics that might influence cancer risk, and yet large enough to provide stable estimates of site-specific cancer mortality. An initial evaluation confirms this opinion, and we have begun to use the county data for studies to formulate and test hypotheses pertaining to high-risk groups. This chapter summarizes some preliminary findings that will be refined and expanded as we gain experience with this resource.

### DEMOGRAPHIC CHARACTERISTICS

#### Urban-Rural and Socioeconomic Differences

The wealth of demographic data characterizing county populations permits detailed analyses of characteristics that may influence the geographic variation of

cancer. Preliminary results are available on the effects of urbanization and social class, based on a comparison of counties with extreme values for these factors. Using census-derived data, we compared the mortality rates for the 957 counties listed as 100 percent rural in the 1950 census with the rates for the 13 counties listed as 100 percent urban. Since urbanization is related to social class, we removed these areas from the total 3,056 counties in the United States, and ranked the remaining counties by social class, based on the median number of school years completed by the adult population. We then compared the rates in the top 10 percent of counties ranked on this variable with those in the bottom 10 percent. The 35 cancer sites were then ordered according to the magnitude of the urban-rural ratios (Table 1) and social-class ratios (Table 2). Most of the urban-rural differences are in the direction expected from previous studies [2,3], but in both sexes a surprisingly large urban effect is observed for cancers of the nasopharynx, larynx, colon, and rectum. The social-class ratios also are as anticipated for many tumors [4,5], but with certain peculiarities. In some instances, urbanization may confound the social-class associations, or the extremes may not be representative of the total social-class gradient. To evaluate these possibilities, the age-adjusted death rates were calculated for cross-classified categories of social-class and urbanization for the entire country. Table 3 shows examples of these analyses. Several interesting associations emerge from these more detailed classifications. Positive social-class and urbanization effects are seen for breast cancer and Hodgkin's disease (HD) in females, whereas the urbanization effect for colon cancer disappears when we control for social-class differences. Noteworthy also is the lack of either effect for stomach cancer, which confirms the unexpected lack of association noted when the extremes on these variables are compared.

The patterns for skin cancer mortality in Tables 1 and 2 illustrate potentialities for cancer control. Skin cancer other than melanoma is strongly and inversely related to both social class and urbanization, but no gradients are observed for melanoma. If both tumors have the same cause (sunlight), perhaps the discrepancy is related to variations in treatment and survival. Further studies should evaluate the possibility that segments of the population are experiencing delays in the diagnosis and adequate treatment of an essentially curable cancer; if so, control measures should be instituted.

Thus far, we have moved from demographic variables to cancer mortality. The reverse approach is illustrated in Figure 1 by the geographic distribution of mortality from cancer of the uterine cervix among white women. There is an obvious clustering of high rates in counties in the southeastern portion of the United States. Socioeconomic and urbanization data for the groups of counties having very high rates and for the total United States are given in Table 4. These data suggest that the excess mortality in the southeastern United States can be attributed to the predominance of this cancer in the rural lower socioeconomic classes.

TABLE 1

Urban-rural ratios of age-adjusted cancer mortality rates<sup>a</sup> among whites in the contiguous United States, according to cancer site and sex, 1950-1969.

Male		Female	
Site	Urban/rural	Site	Urban/rural
Esophagus	3.08	Esophagus	2.12
Larynx	2.96	Rectum	2.11
Mouth and throat	2.88	Larynx	1.92
Rectum	2.71	Nasopharynx	1.66
Nasopharynx	2.17	Lung	1.64
Bladder	2.10	Breast	1.61
Colon	1.97	Bladder	1.58
Lung	1.89	Other endocrine glands	1.52
Breast	1.77	Ovary	1.52
All malignant neoplasms	1.56	Colon	1.51
Thyroid gland	1.56	Non-Hodgkin's lymphoma	1.42
Other endocrine glands	1.53	Hodgkin's disease	1.39
Stomach	1.45	Thyroid	1.38
Kidney	1.44	All malignant neoplasms	1.36
Non-Hodgkin's lymphoma	1.39	Stomach	1.35
Other and unspecified	1.38	Pancreas	1.34
Connective tissue	1.35	Mouth and throat	1.29
Pancreas	1.34	Connective tissue	1.28
Biliary passages and liver (primary)	1.34	Brain	1.26
Salivary glands	1.31	Multiple myeloma	1.25
Hodgkin's disease	1.25	Other and unspecified	1.17
Brain	1.21	Leukemia	1.15
Multiple myeloma	1.12	Kidney	1.12
Nasal sinuses	1.10	Salivary glands	1.12
Leukemia	1.07	Nasal sinuses	1.08
Bone	1.05	Biliary passages and liver	1.04
Melanoma of skin	1.01	Corpus uteri	1.00
Prostate	.96	Cervix uteri	1.00
Testis	.96	Eye	.92
Eye	.77	Bone	.89
Other skin	.67	Melanoma of skin	.87
Lip	.57	Other skin	.65
		Lip	.29

<sup>a</sup>Rates were calculated for 100 percent urban and 100 percent rural counties.

TABLE 2  
Social-class ratios of age-adjusted cancer mortality rates<sup>a</sup> among whites in the  
contiguous United States, according to cancer site and sex, 1950-1969

Male		Female	
Site	Social-class ratio (high/low)	Site	Social-class ratio (high/low)
Rectum	2.13	Rectum	1.67
Thyroid gland	1.72	Breast	1.54
Colon	1.67	Ovary	1.52
Bladder	1.67	Other endocrine glands	1.52
Other endocrine glands	1.59	Non-Hodgkin's lymphoma	1.49
Connective tissue	1.54	Colon	1.45
Kidney	1.49	Connective tissue	1.43
Esophagus	1.49	Multiple myeloma	1.39
Non-Hodgkin's lymphoma	1.37	Hodgkin's disease	1.37
Multiple myeloma	1.35	Brain	1.35
Mouth and throat	1.19	Nasopharynx	1.28
Testis	1.18	Lung	1.27
Breast	1.18	Bladder	1.19
Brain	1.18	All malignant neoplasms	1.18
All malignant neoplasms	1.16	Kidney	1.14
Hodgkin's disease	1.14	Eye	1.12
Leukemia	1.11	Pancreas	1.10
Lung	1.10	Thyroid gland	1.09
Nasopharynx	1.10	Leukemia	1.06
Prostate	1.09	Stomach	1.03
Stomach	1.09	Nasal sinuses	1.01
Larynx	1.02	Esophagus	.97
Pancreas	1.01	Corpus uteri	.94
Melanoma of skin	.98	Biliary passages and liver	.94
Nasal sinuses	.96	Salivary glands	.86
Biliary passages and liver	.88	Other and unspecified	.85
Eye	.87	Melanoma of skin	.85
Other and unspecified	.85	Mouth and throat	.78
Salivary glands	.83	Cervix uteri	.74
Lip	.81	Bone	.69
Bone	.81	Larynx	.67
Other skin	.53	Other skin	.47
		Lip	.32

<sup>a</sup>See text for method of choosing high and low social-class counties.

TABLE 3

Age-adjusted mortality rates (1950-1969) for selected cancers among whites in counties, grouped according to the percent of the population living in an urban area and the median number of years of school completed by the adult population (1960)

Site and sex	Years of schooling	Percent urban		
		0-39.9	40-69.9	70-100
Colon (females)	≤ 8.5	11.52	11.07	9.23
	8.6-10.0	14.88	14.88	18.71
	> 10.0	16.04	15.36	16.72
Esophagus (males)	≤ 8.5	2.13	2.56	3.09
	8.6-10.0	2.46	3.12	5.65
	> 10.0	2.69	3.24	5.07
Breast (females)	≤ 8.5	17.17	18.05	16.84
	8.6-10.0	21.55	22.17	27.32
	> 10.0	23.42	24.03	28.28
Hodgkin's disease (females)	≤ 8.5	0.97	1.02	0.79
	8.6-10.0	1.18	1.22	1.45
	> 10.0	1.28	1.28	1.44
Nasopharynx (males)	≤ 8.5	0.32	0.39	0.19
	8.6-10.0	0.27	0.30	0.53
	> 10.0	0.24	0.30	0.41
Stomach (males)	≤ 8.5	12.31	12.59	14.47
	8.6-10.0	14.09	13.64	16.88
	> 10.0	13.58	13.77	16.30

#### North-South Variation

Variation in cancer mortality by latitude has always intrigued etiologists, particularly those seeking evidence of infectious agents. A constant dilemma in such analyses has been the inability to separate North-South differences from urban-rural or social-class effects. Our efforts to clarify the associations are illustrated by two cancer sites.

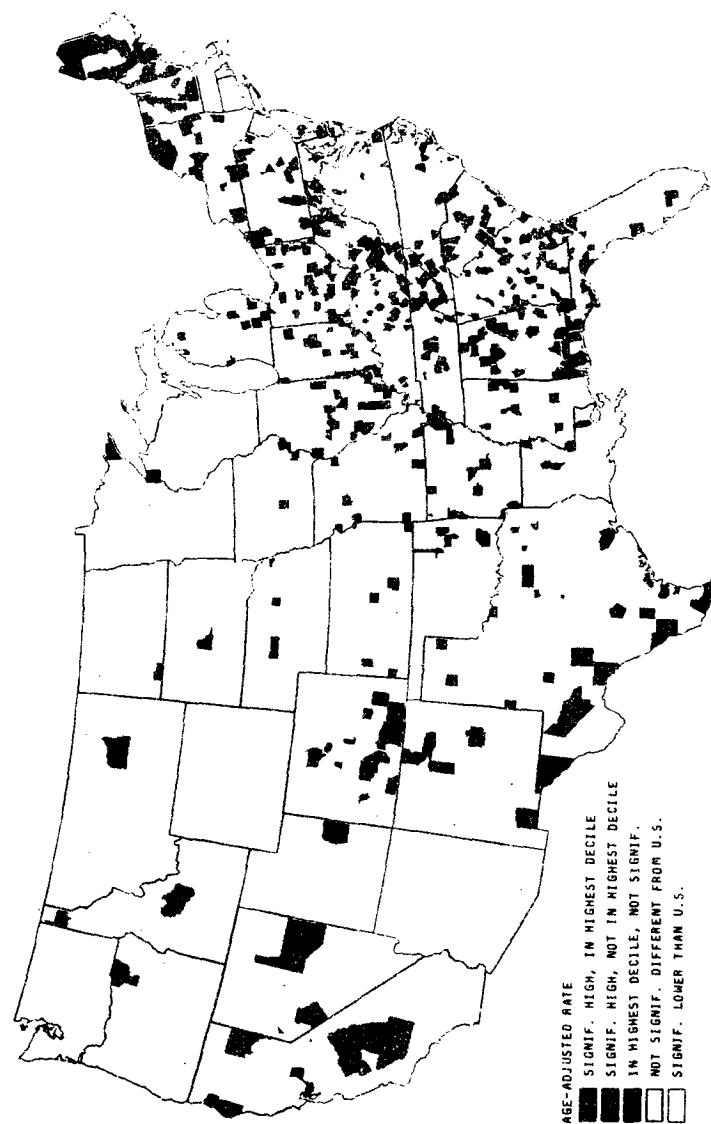


FIGURE 1. Mortality from cancer of cervix among white females  
by U.S. county, 1950-69.

TABLE 4

Measures of urbanization and socioeconomic class (1960) for the total United States, and for counties with an upper-decile mortality rate for cervical cancer among white females, 1950-1969

Area	Percent urban <sup>a</sup>	Median school yrs. <sup>b</sup>	Median family income(\$)
Total United States	69.9	10.2	5,741
Counties in highest decile for cervical cancer, statistically significant <sup>c</sup>	52.9	9.4	4,402
Counties in highest decile for cervical cancer, not statistically significant	25.4	8.7	3,316

<sup>a</sup>Percent of the population living in urban areas (1960 census definition).

<sup>b</sup>Median number of years of schooling completed by the adult population, 25 years old and older.

<sup>c</sup>Significantly different from the rate for the total United States ( $p < 0.05$ ).

Melanoma previously has been related to latitude (sunlight exposure) [6], and Figure 2 confirms an excess in the South in mortality from this tumor. This figure illustrates the distribution of rates by state economic areas. There are 506 of these areas, which are groups of counties with similar geographic, demographic, and economic characteristics. We found these units provide more stable rates for relatively uncommon cancers than do counties. Figure 3 illustrates mortality rates from melanoma for eight zones of latitude, standardized for age, urbanization, and social-class differences. There is a striking trend of increasing mortality as one moves from North to South. Also presented are the relationships for HD, a neoplasm of unknown etiology, previously shown to predominate in the North [7]. As shown for white females, there is a gradient of declining mortality from North to South independent of urbanization and social class. Since the bimodal age distribution of HD suggests epidemiologic heterogeneity, the data are being reanalyzed by age group.

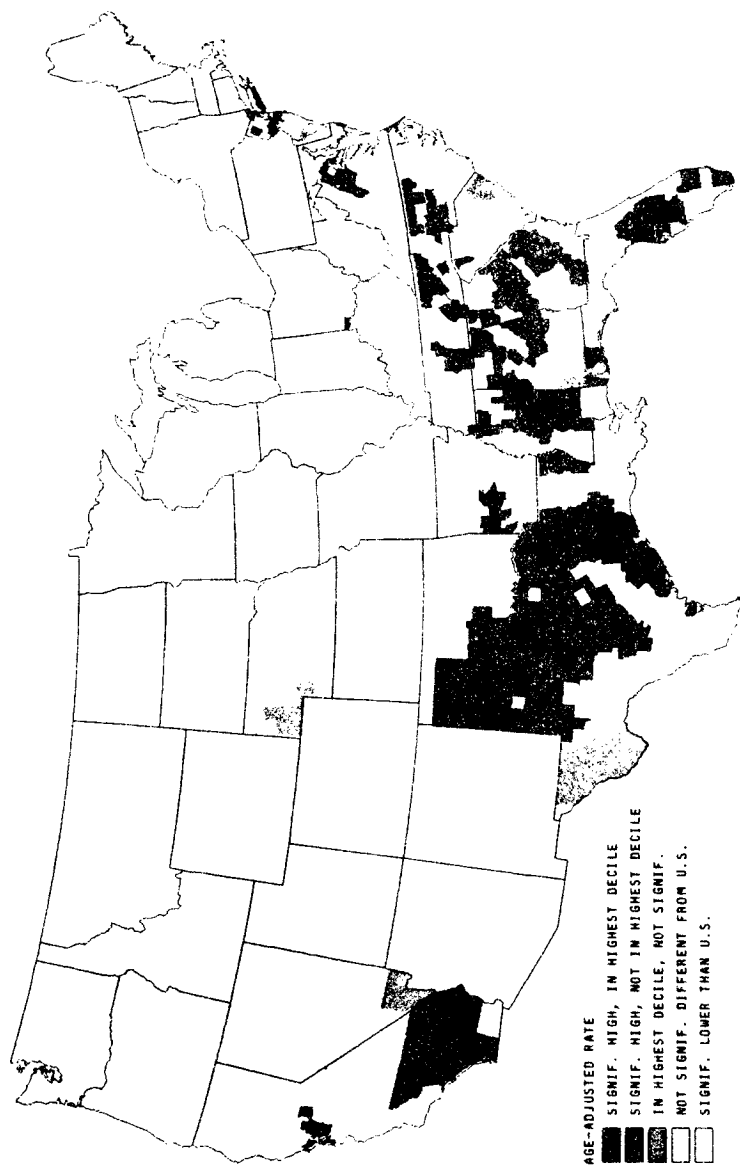


FIGURE 2. Mortality from skin melanoma among white males by U.S. state economic area, 1950-69.



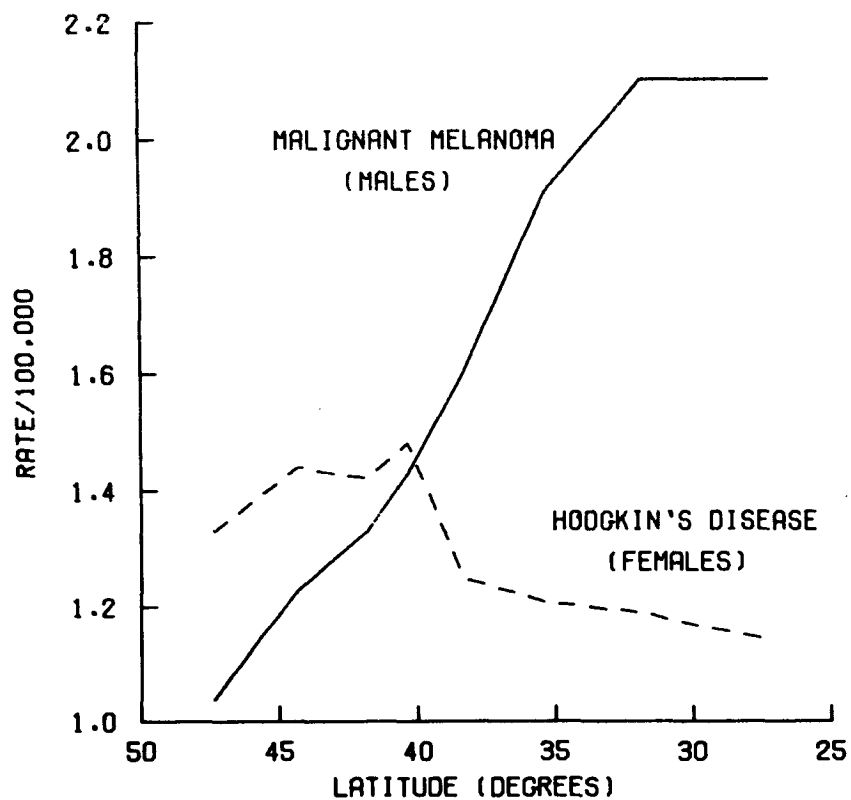


FIGURE 3. Mortality rates for malignant melanoma (males) and Hodgkin's disease (females) according to latitude in United States, 1950-69.

### Concomitant Variation

Detection of a strong geographic correlation between different cancers may suggest a related etiology and potentiality for control programs targeted toward certain constellations of cancer. Pearson product-moment correlation coefficients were calculated between cancer sites for white males and females in all 3,056 counties. We computed two sets of coefficients: 1) the first allows each county to contribute equally to the comparison and 2) the other is a weighted correlation, with the weight being the proportion of the total U.S. population (race- and sex-specific) in the individual counties. The weighted correlation has the advantage of increased stability because of the greater contribution from large counties with more stable rates, and the disadvantage of accentuating urban correlations and masking those that are unrelated to urbanization. When the results from the two methods are synthesized, we find among males that cancers of the lung, larynx, and mouth and throat are highly correlated and might be thought of as a "smoking complex." Another group of correlated sites consists of cancers of the colon, rectum, esophagus, and bladder, and might be considered an "urbanization complex." Although bladder and esophageal cancers correlate also with the smoking complex, the association is not as strong as with the urbanization group. This finding is consistent with evidence for independent smoking and urbanization components for these two cancers [8,9]. Stomach and kidney cancers correlate with the urban complex, but at lower levels. Pancreatic cancer correlates with the smoking complex, but also at a considerably lower level. Further correlations include melanoma with other skin cancers, and non-Hodgkin's lymphoma with several sites in the urban complex (particularly bladder cancer). On the other hand, no impressive between-site correlations were found for leukemia, testicular cancer, or prostatic cancer.

Among white females, cancers of the colon, rectum, breast, and ovary are all highly correlated, and probably reflect both urbanization and social-class determinants of these tumors. Stomach cancer, bladder cancer, and lymphomas join this complex at successively lower magnitudes of association. However, contrary to the experience in males, esophageal cancer is not part of this urban complex, but correlates mainly with lung and pancreatic cancers to form a possible "smoking complex" for women. Notably absent from this complex are cancers of the oropharynx and larynx, possibly underscoring the interaction of heavy alcohol consumption with smoking in the induction of these tumors, particularly in males [10]. In women, mouth and throat cancer correlates with melanoma, other skin cancer, and cervical cancer—a complex of tumors with a lower socioeconomic class, southern predominance.

One provocative finding involved two cancers of obscure etiology—multiple myeloma and brain tumor. In the unweighted analysis, these cancers had the strongest correlation achieved by white males ( $r = 0.5$ ). This association was not present among white females, but was one of the few detected among nonwhite

males (the analysis in nonwhites was hindered by small county populations). In the weighted analysis, the myeloma-brain tumor correlation remained, but at a greatly reduced level (0.19). This reduction in the magnitude of the correlation can be traced to two factors. First, the magnitude of the unweighted coefficient is artifactually inflated because a few very small counties have very high rates for both tumors. When these counties are eliminated (or given small weights), the association remains, but at a much lower level. Second, the association is generally much stronger in the smaller, rural counties that do not carry much weight in the weighted correlations. These analyses do not necessarily signify that the two cancers are rural diseases. Indeed, the rates are higher in cities than in rural areas. These observations indicate, however, that in rural settings brain tumors and multiple myeloma among males may vary concomitantly. This correlation may be related in some way to the reported excess of both tumors in farmers [11,12], but the finding remains to be clarified by further study.

For further clues to etiologic factors and control measures, county correlations were made between the male and female cancer rates for whites. Both the unweighted and the weighted correlations show an impressive range in the magnitude of the coefficients (Table 5). The low correlations for some rare tumor sites may be due to artifact, but this explanation is unlikely to apply to the low values obtained with both methods for cancers of the larynx and kidney, HD, multiple myeloma, and leukemia. Also noteworthy are the high correlations for cancers of the stomach, colon, rectum, and lung.

## ENVIRONMENTAL EXPOSURES

### Hypothesis Testing

Although population-based mortality data are a crude means of testing hypotheses concerning public health hazards, geographic correlations with environmental measurements can be done quickly and inexpensively, and may be a valuable first step in evaluation of possible dangers. For example, cancer mortality patterns were not unusual among people residing in counties where drinking water is contaminated by asbestos [13], or where homes are built upon radioactive tailings from uranium mines [14]. Caution is necessary, however, since the latent period between exposure and disease may not have been sufficiently long for manifestation of risk. On the other hand, in a recent survey of counties where the chemical industry is highly concentrated [15], we found among males, excessive mortality from cancers of the bladder, lung, liver, and certain other sites. The correlation could not be explained by confounding variables such as urbanization, socioeconomic class, or employment in nonchemical industries. If the excess cancer mortality in

TABLE 5

Unweighted and weighted correlation coefficients ( $r$ )<sup>a</sup> between white men and women, using age-adjusted sex-specific mortality rates for individual counties of the contiguous United States, according to cancer site, 1950-1969

Site	Unweighted $r$	Weighted $r$
Lip	-.01	.01
Salivary gland	.03	.05
Nasopharynx	.01	.08
Mouth and throat	.14	.25
Esophagus	.12	.39
Stomach	.34	.77
Colon	.39	.80
Rectum	.41	.81
Liver and biliary passages	.13	.39
Pancreas	.09	.37
Nasal sinus	-.02	.03
Larynx	.07	.19
Lung	.24	.62
Breast	.03	.20
Kidney	.06	.19
Bladder	.12	.45
Melanoma	.07	.24
Other skin	.14	.31
Eye	.00	.02
Brain	.04	.28
Thyroid	.01	.12
Other endocrine	.04	.06
Bone	.02	.11
Connective tissue	.01	.05
Hodgkin's disease	.06	.18
Non-Hodgkin's lymphoma	.08	.34
Multiple myeloma	.01	.11
Leukemia	.10	.21
Other and unspecified	.24	.57
All sites combined	.45	.82

<sup>a</sup>Pearson product-moment correlation coefficients. In the unweighted comparison each of the 3,056 counties contributed equally. In the weighted comparison, the weights used were the proportion of the total population that resided in each county during the 20-year period.

these areas were due to industrial exposures, the actual risk of cancer among certain chemical workers must be very high. Indeed, the correlation was limited to counties associated with specific categories of the chemical industry; many involve known occupational hazards, whereas others suggest new leads to chemically induced cancer in man.

### Hypothesis Formulation

The major contribution of the county resource probably will be to identify geographic clusters suggesting etiologic clues, which can then be pursued by analytic studies. The distribution of stomach cancer was one of the first examined, since the expected social-class gradient was absent (*see above*), suggesting important confounding variables. Figure 4 shows the geographic distribution of stomach cancer among white males. Elevated mortality is prominent in the major cities and in areas characterized by low social class (e.g., certain counties in Pennsylvania and Kentucky). Overshadowing those areas, however, is an impressive cluster of excessive mortality in primarily rural counties in the north-central region (Minnesota, the Dakotas, Michigan, and Wisconsin). Concentrated in these areas are people of Russian, Austrian, Scandinavian, and German descent. In fact, the 306 counties with the highest rates (highest decile) had three times as many first- and second-generation Finns, Austrians, and Russians as expected, and 40 to 60 percent more Norwegians, Swedes, and Germans than expected, based on the national percentages for these ethnic groups. Susceptibility of these migrant groups to stomach cancer would be compatible with the high incidence of this tumor in their countries of origin [16,17]. The smaller cluster in New Mexico and Colorado seems consistent with reports of elevated stomach cancer rates among Spanish-Americans in this area [18]. Thus, although urbanization and socioeconomic factors affect mortality from stomach cancer, ethnicity seems to be the major determinant of geographic variation within the United States.

A different array of geographic clustering is seen with bladder cancer mortality among white males (Figure 5). The clusters of elevated mortality correlate well with industrial exposures previously linked to this tumor. Since it seems likely that new occupational factors remain to be identified, the clusters can provide clues to industries that should be evaluated. To help isolate these areas, we selected a group of counties with the following criteria: 1) a significantly high mortality from bladder cancer among males compared to the national rate, 2) a greater male-to-female ratio of bladder cancer than found nationally, and 3) a lung cancer rate among males not significantly different than the national average (to reduce the confounding influence of cigarette smoking). The industrial makeup of this group of counties was determined from the 1950 census of workers by county employed in various industries. The percentage of workers employed in 41 separate industries was calculated for the

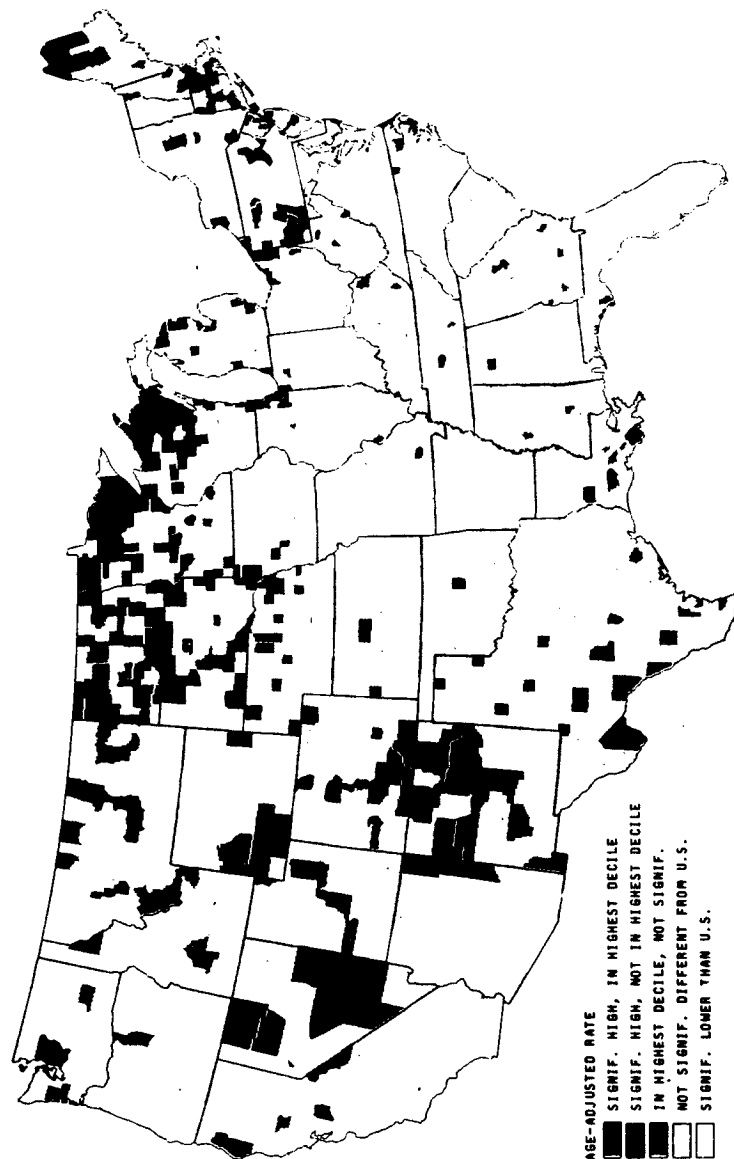


FIGURE 4. Mortality from stomach cancer among white males  
by U.S. county, 1950-69.

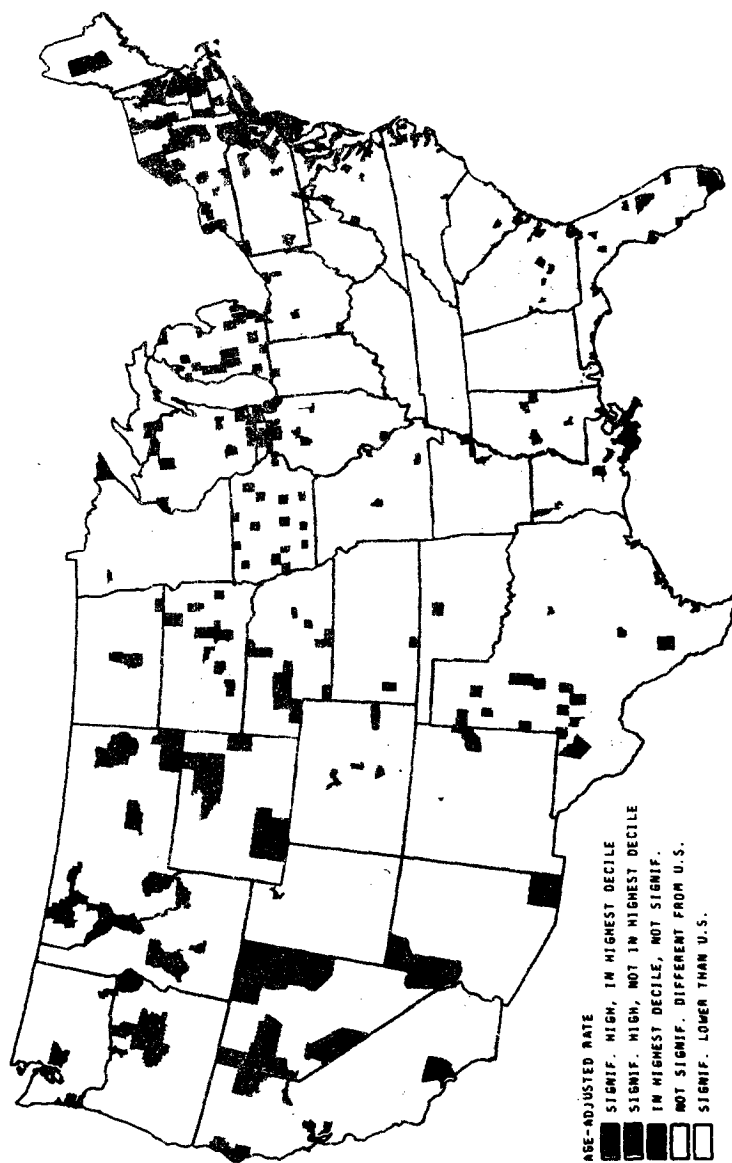


FIGURE 5. Mortality from bladder cancer among white males by U.S. county, 1950-69.

study counties and compared with corresponding percentages for the entire United States. Statistically significant differences occurred for only six industrial categories (Table 6). For three categories, the percentage employed in the study counties was significantly lower than the national experience, but the industries were mainly in rural areas, where the risk of bladder cancer is low. However, the percentage of workers in the study counties was significantly high for three categories: machinery manufacturing (except electrical), electrical machinery manufacturing, and motor vehicle manufacturing. These industries have not been previously implicated in bladder carcinogenesis, and would be a logical place to search for occupational determinants. Suspicions regarding the automobile industry were deepened by recent results from the Third National Cancer Survey, 1969-1971 [19]. Detroit had the highest incidence rate for bladder cancer (but only the fifth highest rate for lung cancer) among white men in the seven cities and two states participating in the Survey. Wayne County (Detroit) was excluded from our correlation study because of a significantly elevated rate for lung cancer. However, its mortality rate for bladder cancer is significantly high among men, but not among women.

TABLE 6  
Industrial categories in which the percent of persons  
employed in counties with a high bladder cancer risk<sup>a</sup>  
differed significantly ( $p < 0.05$ ) from the percent of  
such persons employed nationwide

Type of industry	Total U.S. (expected)	High-risk counties (observed)	Observed/ expected
Agriculture	15.5	4.2	0.3
Mining	2.2	0.3	0.1
Manufacturing	27.0	42.2	1.6
Furniture, lumber, wood	2.7	1.4	0.5
Machinery (except electrical)	2.8	6.3	2.3
Electrical machinery	1.3	2.8	2.2
Motor vehicles	1.9	4.8	2.5

<sup>a</sup>See text for method of selecting "high-risk" counties.



### Unusual Counties

Because of the many comparisons involved with data for 3,056 counties over 20 years, it may be dangerous to single out a particular county or even a small group of counties for special attention. In certain situations, however, the unusual mortality experience of a county would seem to warrant further investigation. For example, Salem County, New Jersey, leads the nation in bladder cancer mortality among white men. The excess risk is surely due to occupational exposures, since about 25 percent of the employed persons in this county work in the chemical industry, primarily the manufacturing of organic chemicals with a potential for causing bladder tumors. This finding indicates the need for surveys of cancer risk and programs in cancer control among workers in this area.

Another rationale for studying individual counties is the identification of a highly unusual occurrence not easily explained. For example, in Nebraska there are two adjacent counties (Butler and Colfax) that have very high death rates for colon cancer. Although this tumor predominates in the upper social class and urban northeast, these two counties are predominantly low social class, rural, and midwestern. Over 25 percent of the population in these counties are foreign born or have foreign-born parents, mainly of Czechoslovakian descent [20]. The rates for colon cancer are reportedly not high in Czechoslovakia [17], but further studies of colon cancer in these Nebraskan counties seem warranted.

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## DISCUSSION

**Dr. Peters** noted that "bedroom communities"—counties on the fringes of urban areas—might be expected to have cancer patterns similar to those of urban areas. **Dr. Hoover** responded that this was generally so, and that such communities are not necessarily contiguous to the urban areas. For example, Dade County, Florida (Miami), with high cancer rates for a number of sites, could be pictured as the bedroom community for New York, Chicago, or a number of Northeastern and Midwestern cities.

**Dr. Mack** commented that Dr. Hoover's county correlation studies between cancer mortality and environmental-demographic exposures represent a prime example of what record-linkage can accomplish.

*William J. Blot*